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ORIGINAL ARTICLE

Changes in first-line injectable disease-modifying therapy for multiple sclerosis: predictors of non-adherence, switching, discontinuation, and interruption of drugs

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Abstract This study was aimed to describe changes of Disease-Modifying Treatments (DMT) in an Italian cohort of patients with multiple sclerosis (MS) and to identify predictors of therapeutic modifications. Patients with MS and treated with the first-line injectable DMT (interferons-IFNs or glatiramer) between 1/7/2009 and 31/10/2012 were selected from administrative databases of the MS Center of Cagliari (Sardinia, Italy). Socio-demographic, therapeutic, and clinical information was collected in the 6 months preceding the index date. All patients were followed for 36 months to evaluate therapeutic changes in terms of non-adherence, switch, temporary discontinuation, and permanent interruption. Predictors of changes were estimated by multivariable regression models. Data on 1698 patients were collected: glatiramer was prescribed in 27% of cases, IFNβ-1b in 22%, IFNβ-1a-im in 20%, IFNβ-1a-sc-44mcg in 19%, and IFNβ-1a-sc-22mcg in 12%. Non-adherence was observed in 25% of cases, therapeutic switch in 30%, discontinuation in 37%, and permanent interruption in 28%. The risk of non-adherence was higher for IFNβ-1b, compared with IFNβ-1a-im (adjOR = 1.73). Therapeutic switch occurred especially in patients recently diagnosed (each year from diagnosis causes a decrease of this risk adjHR = 0.97); the risk of discontinuation was higher with EDSS = 4–6 and 7–9 (adjHR = 1.52 and 4.42, respectively). The risk of permanent interruption increased with the augmentation of disability (adjHR = 1.67 and 5.43 for EDSS 4–6 and 7–9). This study mirrored a detailed framework of DMT prescription and identified factors related to changes in the MS therapy. These findings could support healthcare providers in the evaluation and maximization of benefits associated with a long-term DMT.

Keywords Multiple sclerosis · Disease-modifying drugs · Adherence · Switch · Discontinuation · Interruption

Introduction

Multiple sclerosis (MS) is an autoimmune disease in a stage of rapid progress in terms of new drugs recently approved (i.e., natalizumab, fingolimod, alemtuzumab, teriflunomide, and dimethyl fumarate) or will be launched in the near future (i.e., laquinimod, ocrelizumab, and daclizumab) [1]. These new therapeutic opportunities are adding into a complex therapeutic armamentarium which consists, in most cases (in particular in relapsing remitting forms of MS), of a first-line therapy with injectable DMT (disease-modifying treatments) and following with the second-line therapies (different DMT or immunosuppressive drugs).

The first-line DMT should modify the natural history of disease by reducing frequency and severity of relapses, decreasing number of new brain lesions, and slowing disability progression. This class consists of five drugs: interferon (IFN) β-1a im, administered intramuscularly (im) once weekly, IFNβ-1a sc-22mcg and IFNβ-1a sc-44mcg, both administered subcutaneously (sc) three times

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weekly, and IFNβ-1b sc and glatiramer acetate, both administered subcutaneously daily. All these injectable DMTs are indicated for chronic therapy [2].

Various head-to-head trials did not show great differences among these agents in terms of efficacy and safety for subjects affected by relapsing remitting MS [3]. However, in clinical practice, various factors, related to patients or to physicians, could play an important role in the choice of a specific DMT and in the persistence and adherence to a given therapy [4], thus may compromise the clinical outcome of these therapies and may drive the physician to choice a second-line agents, although the limited information on their safety and their high costs. Therefore, an inadequate treatment with DMT could result in a progression of the disease with a higher rates of relapses and hospitalizations [5] and, consequently, in greater healthcare resource utilization [6]. Conversely, the minor risk of relapses in adherent subjects leads to a decrease in direct and indirect costs to treat disease exacerbations [7]; moreover, adherent patients reported a better quality of life and fewer neuropsychological issues rather than non-adherent patients [8].

Several pharmaco-epidemiological studies, performed on database or questionnaires, investigated the pattern of use of DMTs and found factors associated with therapy modifications. These studies showed that the adherence to these agents decreases over time, and around half of patients discontinued their DMT within 2 years of starting therapy [4, 9]. Moreover, an analysis based on a US prescription database found that the rate of switch did not significantly differ among injectable DMTs, whereas discontinuation was higher for subcutaneous preparations rather than intramuscular one, and IFNβ-1b sc had the lowest persistence among analysed DMTs [10].

Across the world, MS affects approximately 2.3 million of individuals, 600,000 of whom are in Europe and 55,000 in Italy [11]. Among Italian regions, Sardinia presents the highest frequency of MS, probably due to genetic and environmental influences: a recent epidemiological study in the south-western Sardinia estimated a prevalence of 210.4/100,000 and an incidence of 9.7/100,000 [12].

Despite this particular epidemiology, to the best of our knowledge, no analysis of drug utilization of different agents used in this disease exists for Sardinia and few such studies are available for other Italian regions [13]. Therefore, the aim of this study was to describe the pattern of DMT use in terms of changes of DMT in an Italian cohort of patients with MS and to identify predictors of therapeutic modifications.

Methods

Data sources

We performed an observational historic cohort study based on administrative databases of the Multiple Sclerosis Center of Cagliari Local Health Authority (Sardinia Region, Italy).

Using a record linkage of different databases, we collected socio-demographic, therapeutic, and clinical information. The "file F database" was explored to retrieve information on DMT prescriptions: dispensing date, ATC (Anatomical-Therapeutic-Chemical ver. 2014) code, and number of packages with the relevant days of therapy. For each patient, the following clinical data were collected: date of the first MS diagnosis and EDSS (Expanded Disability Status Scale) score at the first diagnosis.

To assurance patient privacy, each subject was assigned an anonymous univocal numeric code by Local Health Authority. No identifiers or data that permitted identity the patient in a direct or indirect way were provided to the researchers. In accordance with national regulations [14] regarding the conduct of observational analysis, the present study has been notified to the local Ethical Committee of the participating Local Health Authority.

Cohort selection

Patients with an MS diagnosis and treated with an injectable DMT (interferons-IFN, ATC: L03AB07/08 or glatiramer acetate, ATC: L03AX13) in the period 1st July 2009–31th October 2012 were included in the study cohort. The first DMT prescription observed in the recruitment period represented the index date and the index drug for each subject. In the 6 months preceding the index date, patients were characterized for their clinical severity (according EDSS value) and were distinguished in established or naïve for treatment according to the presence/absence of a DMT prescription. All patients were observed during the 36 months following the index date.

Measures of changes

To detect changes in therapy, we analysed four different modification measures: lack of adherence, therapeutic switch, temporary discontinuation, and definitive interruption of any drugs. Adherence was evaluated using the medication possession ratio (MPR) [15], which is calculated as the sum of the days supplied divided by all days of the follow-up period; for the last supply, the days in excess of the period of observation were excluded. We considered non-adherent therapy when the MPR was <80% and we

performed this analysis only for patients without switches in the observation period. Therapeutic switch was considered as a change of injectable DMT during patient therapeutic history. Temporary discontinuation was defined as the absence of drug refills for six consecutive months following the days covered with the last observed prescription, whereas definitive interruption was defined as the absence of drug supply in the 12 months after the last prescription coverage.

Statistical analysis

Continuous variables were reported as mean and standard deviation (median and range as appropriate), whereas categorical variables were expressed as numbers and percentages and compared using Chi-square test. To explore the association between covariates and the risk of therapeutic switch, temporary discontinuation, or definitive interruption, Cox proportional hazards multivariable regression models were performed. To investigate variable associated with risk of lack of adherence, a logistic regression model was used. Schoenfeld residual analysis was used to validate the proportional hazards assumption.

Two-tailed p values less than 0.05 were considered significant. All analyses were performed using STATA SE, version 12.0.

Results

We selected a cohort of 1698 patients with MS and at least a prescription of an injectable DMT during the observation period. Females were 69% of the cohort, with a mean age of 40.0 ± 10.7 year. The mean (±standard deviation, SD) of disease duration was 5.9 ± 6.3 years and the most part of the cohort had a low disability (EDSS ≤3 in 79% of cases). Naïve patients represented the 36% of sample. The index DMT was IFNβ-1a sc-22mcg in 12% of the cohort, IFNβ-1a im in 20%, glatiramer acetate in 27%, IFNβ-1a sc-44mcg in 19%, and IFNβ-1b sc in 22%. By comparing the characteristics of each therapeutic group, no significant differences were found, with the exception of the EDSS that appeared higher in patients treated with glatiramer acetate (EDSS 4–6 in 18% of cases) or IFNβ-1b sc (EDSS 4–6 in 12%) rather than other DMTs (Table 1).

During the follow-up, 1187 patients (70% of the cohort) did not change their drug and out of these 35% resulted not adherent. Drug switch occurred in 30% of the overall cohort, temporary discontinuation of therapy in 37%, and permanent interruption in 28%. Interferon β-1a sc 22 mcg and IFNβ-1b sc showed the highest percentage of non-adherence (41%), whereas glatiramer acetate the lowest rate of lack of adherence (29%). The rate of therapeutic switch ranged from 25% for therapy started with IFNβ-1a im (25%) to 33% with IFNβ-1b sc. Temporary discontinuation was more frequent among subjects with IFNβ-1a im (44%) rather than other DMTs. Permanent interruption rate ranged from 21% for IFNβ-1a sc 22 mcg to 35% for IFNβ-1a im (Table 2).

The age increase of subjects appeared to have a protective effect for three of four analysed changes: the risks of non-adherence (adjOR = 0.98; 95% CI = 0.97–1.00), therapeutic switch (adjHR = 0.97; 95% CI = 0.96–0.98), and temporary discontinuation (adjHR = 0.98; 95% CI = 0.97–0.99) significantly decreased with an augmentation of 1 year age (Table 3).

The risk of non-adherence was higher in subjects treated with IFNβ-1b sc (adjOR = 1.73; 95% CI 1.14–2.62) compared with IFNβ-1a im. Moreover, this risk was lower in man rather than female (adjOR = 0.73; 95% CI 0.55–0.96) and in established (adjOR = 0.59; 0.43–0.79) compared with naïve patients. Furthermore, it was higher in the presence of an EDSS = 4–6 (adjOR = 1.78; 95% CI 1.17–2.71) as well as this risk increased with longer disease duration (an increase of adjOR = 1.03 for each year elapsed from the diagnosis, Table 3).

The risk of therapeutic switch significantly decreased with the increase of length of disease (each year from diagnosis causes a decrease of this risk adjHR = 0.97; 95% CI 0.95–0.99, Table 3).

Temporary discontinuation risk significantly decreased in man rather than female (adjHR = 0.69; 95% CI = 0.54–0.88) and in established patients (adjHR = 0.64; 95% CI = 0.50–0.82) compared with naïve patients. Furthermore, it was higher in the presence of an EDSS = 4–6 (adjHR = 1.52; 95% CI = 1.08–2.13) and EDSS 7–9 (adjHR = 4.42; 95% CI = 1.59–12.26), both compared with EDSS = 0–3 (Table 3).

Finally, there was a positive trend for the risk of permanent discontinuation at a different EDSS (adjHR = 1.67; 95% CI = 1.19–2.34 for EDSS = 4–6 and adjHR = 5.43; 95% CI = 1.95–15.61 for EDSS 7–9, both compared with EDSS = 0–3. Moreover, this risk was lower in established patients (adjHR = 0.60; 95% CI = 0.46–0.78) compared with naïve patients and in subject treated with IFNβ-1a sc-22mcg (adjHR = 0.64; 95% CI = 0.45–0.91) and 44mcg (adjHR = 0.60; 95% CI = 0.39–0.94), both compared to INFβ-1a im. (Table 3).

Discussion

The present study mirrored a detailed pattern of DMT use among a cohort of Italian (Sardinia) patients with MS. It focused on four therapy modifications (lack of adherence, drug switch, temporary discontinuation, and permanent

Table 1 Socio-demographic, clinical, and therapeutic characteristics of cohort, grouped by index DMT

	Any Drug		INF β-1a im		Glatiramer acetate sc		INF β-1a sc-22mcg		INF β-1a sc-44mcg		INF β-1b sc	
	N	(%)	*N*	(%)	*N*	(%)	*N*	(%)	*N*	(%)	*N*	(%)
	1698	(100)	321	(100)	340	(100)	458	(100)	209	(100)	370	(100)
Age												
Mean ± SD	40.0 ± 10.7		39.9 ± 11.3		43.7 ± 10.4		39.1 ± 10.1		36.2 ± 9.2		40.1 ± 11.0	
Gender												
Female	1167	(69)	226	(70)	232	(68)	314	(69)	145	(69)	250	(68)
Male	531	(31)	95	(30)	108	(32)	144	(31)	64	(31)	120	(32)
Therapeutic history												
Naive	615	(36)	86	(27)	122	(36)	181	(40)	66	(32)	160	(43)
Established	1083	(64)	235	(73)	218	(64)	277	(60)	143	(68)	210	(57)
EDSS												
0–3	1346	(79)	272	(85)	241	(71)	389	(85)	181	(87)	263	(71)
4–6	165	(10)	13	(4)	60	(18)	23	(5)	0	(0)	46	(12)
7–9	5	(0)	0	(0)	2	(1)	9	(2)	0	(0)	19	(5)
n.a.	182	(11)	36	(11)	37	(11)	60	(13)	3	(1)	44	(12)
Years from diagnosis												
Mean ± SD	5.9 ± 6.3		6.1 ± 6.3		7.0 ± 6.0		5.4 ± 6.2		5.3 ± 5.9		5.7 ± 6.7	

DMT disease-modifying treatment, *INF* interferon, *im* intramuscular, *sc* subcutaneous, *EDSS* Expanded Disability Status Scale, *SD* standard deviation, *n.a.* not available

Table 2 Rate of therapeutic changes for each first-line injectable DMT

	Patients		Non-adherence (MPR <80%)*		Therapeutic switch		Discontinuation (<6 months)		Permanent interruption	
DMT	*N*	(%)	*N*	(%)	*N*	(%)	*N*	(%)	*N*	(%)
IFNβ-1a im	340	(20)	93/254	(37)	86	(25)	150	(44)	118	(35)
Glatiramer acetate sc	458	(27)	92/320	(29)	138	(30)	150	(33)	113	(25)
IFNβ-1a sc-22mcg	209	(12)	58/143	(41)	66	(32)	71	(34)	43	(21)
IFNβ-1a sc-44mcg	321	(19)	76/221	(34)	100	(31)	118	(37)	102	(32)
IFNβ-1b sc	370	(22)	101/249	(41)	121	(33)	135	(36)	104	(28)
Any drugs	1698	(100)	420/1187	(35)	511	(30)	624	(37)	480	(28)

DMT disease-modifying treatment, *MPR* medication possession ratio, *INF* interferon, *im* intramuscular, *sc* subcutaneous

* Non-adherence was calculated only on patients without switches

interruption), evaluated for the first-line injectable DMTs (i.e., interferons and glatiramer).

To the best of our knowledge, this analysis represents the first study on pattern of DMT use conducted in the Sardinia area, where the prevalence of MS is highest among Italian regions [12, 16]. The socio-demographic and clinical characteristics of analysed cohort reflected the epidemiology of disease that affects especially young women [11].

Although the socio-demographic and clinical characteristics of patients in each treatment group were similar, some differences in treatment modifications were found. In particular, the lack of adherence was higher in terms of rate and risks for IFNβ-1b sc, rather than other DMTs. Therefore, our study found an almost two-fold risk to lack adherence when the patient started therapy with this IFN; our finding is similar to another study that showed a lowest persistence degree for IFNβ-1b sc [6].

Although our analysis found some variations, in terms of rate, among DMTs for switch (IFNβ-1b sc showed the higher value), temporary discontinuation (IFNβ-1a im showed the higher frequency) and permanent interruption (IFNβ-1a im showed the higher value), these differences were not confirmed by the statistical analysis. Conversely,

Table 3 Predictors of changes in DMT estimated by multivariable regression models (logistic regression model for non-adherence and Cox proportional hazards multivariable regression model for switch, discontinuation, and interruption)

	Non-adherence (MPR <80%)			Therapeutic switch			Discontinuation (<6 months)			Permanent Interruption		
	adjOR	95% C.I.	*p*	adjHR	95% CI	*p*	adjHR	95% CI	*p*	adjHR	95% CI	*p*
Age (+1 year)	**0.98**	**0.97–1.00**	**0.01**	**0.97**	**0.96–0.98**	**<0.01**	**0.98**	**0.97–0.99**	**<0.01**	0.99	0.98–1.00	0.14
Gender												
Female	Ref			Ref			Ref			Ref		
Male	**0.73**	**0.55–0.96**	**0.02**	0.83	0.68–1.01	0.07	**0.69**	**0.54–0.88**	**<0.01**	0.81	0.63–1.04	0.10
DMT												
IFNβ-1a im	Ref			Ref			Ref			Ref		
Glatiramer acetate sc	1.19	0.79–1.80	0.41	0.80	0.59–1.09	0.15	1.31	0.92–1.87	0.13	1.04	0.74–1.47	0.82
IFNβ-1a sc-22mcg	0.87	0.59–1.30	0.50	0.88	0.68–1.16	0.37	0.91	0.64–1.28	0.58	**0.64**	**0.45–0.91**	**0.01**
IFNβ-1a sc-44mcg	1.34	0.84–2.14	0.22	0.83	0.60–1.15	0.26	1.02	0.68–1.54	0.93	**0.60**	**0.39–0.94**	**0.03**
IFNβ-1b sc	**1.73**	**1.14–2.62**	**0.01**	1.01	0.76–1.34	0.95	1.00	0.69–1.45	0.99	0.78	0.54–1.12	0.18
Therapeutic history												
Naive	Ref			Ref			Ref			Ref		
Established	**0.59**	**0.43–0.79**	**<0.01**	1.21	0.97–1.51	0.09	**0.64**	**0.50–0.82**	**<0.01**	**0.60**	**0.46–0.78**	**<0.01**
EDSS												
0–3	Ref			Ref			Ref			Ref		
4–6	**1.78**	**1.17–2.71**	**0.01**	0.95	0.65–1.38	0.78	**1.52**	**1.08–2.13**	**0.02**	**1.67**	**1.19–2.34**	**<0.01**
7–9	5.41	0.58–50.10	0.14	–	–	–	**4.42**	**1.59–12.26**	**<0.01**	**5.43**	**1.95–15.11**	**<0.01**
n.a.	0.87	0.22–3.44	0.84	0.83	0.26–2.58	0.74	0.67	0.16–2.69	0.57	0.38	0.05–2.69	0.33
Years from diagnosis (+1 year)	**1.03**	**1.00–1.05**	**0.03**	**0.97**	**0.95–0.99**	**<0.01**	1.01	0.99–1.03	0.19	1.00	0.98–1.03	0.68

In bold, statistical significant values ($p < 0.05$)

adjOR adjusted odds ratio, *adjHR* adjusted hazard ratio, *95% CI* 95% confidence interval, *Ref* reference, *DMT* disease-modifying treatment, *MPR* medication possession ratio, *INF* interferon, *im* intramuscular, *sc* subcutaneous, *EDSS* Expanded Disability Status Scale

the logistic models showed some factors associated with therapy changes. For example, older age represented a protective factor for three out of four modification measures (except for permanent interruption); this strengthened the value of injectable DMTs in patients that well tolerate these drugs and benefit, and therefore, they are compliant with prescribed therapy. This result is in line with an Australian study reporting that older age is associated with greater treatment persistence [15]. Furthermore, male patients with an established therapy appeared more continuous in treatment (minor risk of temporary discontinuation) than female. Finally, an increase of EDSS was related to a higher risk of temporary or permanent discontinuation of therapy; result consistent with that found by Australian researchers [17]. This finding confirmed that DMTs are useful in early stage of disease when disability is low, while when the disease worsen the second-line treatments (mitoxantrone, natalizumab, alemtuzumab, or fingolimod) become essential [1, 2].

Some main limitations affect our study. First, we did not consider the clinical course of MS (relapsing remitting or progressive) due to unavailability of this information in the database. Second, the absence of reasons of therapeutic modification was not collected in investigated data source (e.g., no information on adverse effect, which represents one of the main reasons of therapy modification, was available) [4, 8]. Finally, our study is affected by usual biases of observational analysis based on administrative databases, especially the uncertainly in the actual administration of drug or the impossibility to track patients who purchase the drug personally. These last two weaknesses should be very limited in our study, as the Italian healthcare system reimburses DMTs for all patients, and these drugs are usually self-administered by patients.

Our study showed no particular differences among the first-line injectable DMTs in terms of changing in therapy, as shown by other studies concerning this therapeutic class [3, 17]. These results demonstrate that the first-line injectable DMTs have a comparable tolerability; therefore, clinicians should choose the starting drug according to the needs of the patient (based on the administration recurrence and the side effects).

In conclusions, the findings of this study could support healthcare providers (clinicians and pharmacists) in the evaluation and maximization of benefits associated with a long-term first-line DMTs, by early identifying subjects that will not-compliant with this therapy. The in-depth knowledge of real-world use of the first-line DMTs is essential to rightly address patients to the second-line drugs (e.g., natalizumab, fingolimod, and others), especially during early times from their launch in the marketing when safety information is lacking and costs are high.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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